

## **II. REMARKS**

### **A. Status of the claims**

Claims 15, 20-23 and 25-26 are currently pending. New claim 26 has been added. Support for new claim 26 can be found throughout the application as originally filed, e.g., at paragraphs 28, 30, 31, 34 and 46 of the specification. It is respectfully submitted that no new matter has been added by virtue of this amendment.

### **B. Rejections under 35 U.S.C. §103**

#### **1. The Manthey reference in view of the Bok reference**

In the Office Action, claims 15 and 20-23 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,184,246 to Manthey et al. in view of U.S. Patent No. 6,096,364 to Bok et al.

This rejection is traversed. Initially, Applicants respectfully submit that, as admitted by the Examiner, the Manthey reference does not teach a method for preventing insulin resistance and the Bok reference does not teach a method of reducing insulin resistance. Accordingly, even if these references were properly combinable (a position refuted by the Applicants) one skilled in the art would not arrive at the presently claimed invention which is directed to methods of treating a mammal having metabolic abnormalities resulting from insulin resistance.

Even if, assuming arguendo, that there was proper motivation to combine the Manthey and the Bok references, Applicants submit that the combined teachings fail to teach or suggest the specific combination of sinensetin, nobilten, tangeretin, heptamethoxyflavone and tetramethylscutellarein as recited in independent claim 15. Further, Applicants respectfully submit that a combination of these references do not teach or suggest a composition comprising

about 9.3% sinensetin, about 35% nobilten, about 11.1% tangeretin, about 33.5% heptamethoxyflavone and about 11.1% tetramethylscutellarein as recited in dependent claim 25

Further, Applicants respectfully direct the Examiner's attention to the Manthey reference at column 6, lines 62-64, which states that "[w]ith the exception of tetra-O-methylscutellarein, surprisingly there was negligible cytotoxicity detected with [other polymethoxyflavone] compounds." In view of this statement, Applicants submit that one skilled in the art would not be motivated to incorporate tetra-O-methylscutellarein (i.e. tetramethylscutellarein) in a pharmaceutical composition to be utilized in the claimed methods, as the Manthey reference teaches that tetra-O-methylscutellarein is cytotoxic.

Regardless of the positions presented above, Applicants further submit that there is no motivation to combine the Manthey reference and the Bok reference, as the individual references are directed to the treatment of unrelated disease states. The Manthey reference describes the use of polymethoxyflavones to inhibit the production of cytokines, which is useful in the treatment of "septic shock, cancer, cachexia, chronic rheumatism, ulcerative colitis, Chron's disease". Manthey et al. at column 2, lines 58-59. The Bok reference describes the use of bioflavonoids to lower blood glucose, which is useful in the treatment of hyperglycemia. The targeted disease states of the Manthey and Bok references do not overlap and therefore one skilled in the art would not be motivated to combine these references.

Also, with respect to the Bok reference, as admitted by the Examiner, the Bok reference fails to teach or suggest tetramethylscutellarein at all, let alone in combination with sinensetin, nobilten, tangeretin and heptamethoxyflavone. Therefore, one skilled in the art would not be motivated to include tetramethylscutellarein into a composition based on the combined teachings of the Bok and Manthey references.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) over the Manthey reference in view of the Bok reference be removed.

**2. The Manthey reference in view of the Bok reference and the Malterud reference**

In the Office Action, the Examiner rejected claim 15 over the Manthey reference and the Bok reference as applied to 15 and 20-23, and further in view of Maltreud et al. ("Inhibitors of 15-lipoxygenase from orange peel". *J Agric Food Chem* (2000 Nov); 48(11):5576-80, printed page 1: Abstract)

This rejection is traversed. For the reasons stated above, a combination of the Manthey reference and the Bok reference do not teach or suggest a method for treating a mammal having abnormalities resulting from insulin resistance by administering the claimed combination of polymethoxyflavones. Further, as presented above, one skilled in the art would not be motivated to combine the Manthey reference and the Bok reference, nor would one of ordinary skill in the art be motivated to include tetramethylscutellarein in a composition based on the teachings of these references.

With respect to the Malterud reference, Applicants respectfully submit that this reference fails to teach or suggest a method for treating a mammal having abnormalities resulting from insulin resistance by administering the specific claimed combination of polymethoxyflavones (i.e., sinensetin, nobilten, tangeretin, heptamethoxyflavone and tetramethylscutellarein). In support of this position, Applicants submit that the Malterud references suggests that sinensetin, nobilten, tangeretin, tetramethylscutellarein and 3, 5, 6, 7, 8, 3, 4 heptamethoxyflavone where somewhat less active than other tested compounds therein.

Therefore, even if the Malterud reference teaches or suggests a method for treating a mammal having abnormalities resulting from insulin resistance (a position refuted by the Applicants), one skilled in the art would not utilize the specifically claimed polymethoxyflavones as Melterud teaches that these compounds are less active than other compounds tested therein for inhibiting soybean 15-lipoxygenase. Accordingly, the Malterud reference fails to cure the deficiencies of the Manthey and Bok references.

Accordingly, Applicants respectfully request that the rejection over the Manthey reference in view of the Bok reference and further in view of the Malterud reference be removed.

### **3. The Pershadsingh reference in view of the Robbins reference**

In the Office Action, claim 25 was rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,087,385 to Pershadsingh et al. in view of U.S. Patent No. 3,867,541 to Robbins et al.

This rejection is traversed. Applicants respectfully submit that the Pershadsingh is directed to thiazolidinedione derivatives which are useful as antiproliferative, anti-inflammatory and antiinfective agents. See Abstract of the Pershadsingh reference. Applicants respectfully submit that the specific claimed combination of polymethoxyflavones (i.e., sinensetin, nobilten, tangeretin, heptamethoxyflavone and tetramethylscutellarein) utilized in the methods of the present invention do not contain a thiazolidinedione moiety, nor are they derivatives of thiazolidinedione compounds. As such, the compounds utilized in the present invention are not encompassed by the thiazolidinedione derivatives described in column 2 of the Pershadsingh reference. Therefore, the Pershadsingh reference does not teach or suggest a method for treating a mammal having abnormalities resulting from insulin resistance by administering a composition which includes the specifically claimed combination of polymethoxyflavones, let alone the specifically recited amounts in dependent claim 25 (i.e., about 9.3% sinensetin, about 35%, about 11.1% tangeretin, about 33.5% heptamethoxyflavone and about 11.1% tetramethylscutellarein).

With respect to the Robbins reference, Applicants submit that this reference also fails to teach or suggest a method for treating a mammal having abnormalities resulting from insulin resistance, let alone utilizing the specifically claimed combination of polymethoxyflavones in the recited amounts in dependent claim 25 (i.e., about 9.3% sinensetin, about 35%, about 11.1% tangeretin, about 33.5% heptamethoxyflavone and about 11.1% tetramethylscutellarein). Therefore, Applicants respectfully submit that the Robbins reference fails to cure the deficiencies of the Pershadsingh reference and a combination of these references do not teach or suggest the presently claimed methods.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) over the Pershadsingh reference in view of the Robbins reference be removed.

#### **4. New Claim 26**

The Examiner is respectfully directed to new claim 26, which recited as follows:

26. A method of treating a mammal having metabolic abnormalities resulting from insulin resistance comprising orally administering a solid or liquid composition comprising an effective amount of a polymethoxyflavone composition consisting essentially of nobiletin and tangeretin, wherein said polymethoxyflavone composition is administered to said mammal in an amount of up to 5000 mg/day or up to 70 mg/kg/day, based on the weight of said mammal, said composition reducing serum insulin levels by at least about 26%.

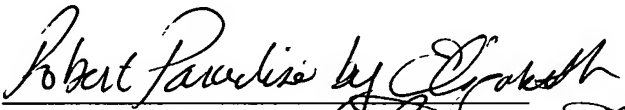
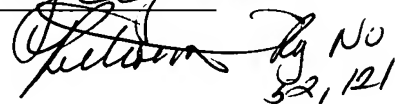
Applicants respectfully submit that the cited prior art, either alone, or in combination, do not teach or suggest all of the recited limitations of claim 26, including the limitation of "... orally administering a solid or liquid composition comprising an effective amount of a polymethoxyflavone composition consisting essentially of nobiletin and tangeretin ..." (Emphasis added).

**III. Conclusion**

It is respectfully submitted that in view of the arguments presented, all rejections have been obviated. An early and favorable action on the merits is earnestly solicited.

According to currently recommended Patent Office policy the Examiner is requested to contact the undersigned in the event that a telephonic interview will advance the prosecution of this application.

Respectfully Submitted,  
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